The clinical conundrum of neonatal seizures

M Levene

There is increasing evidence that neonatal seizures have an adverse effect on neurodevelopmental progression and may predispose to cognitive, behavioural, or epileptic complications later in life. However, given the uncertainty about the efficacy and toxicity of the commonly used anticonvulsants, when and how aggressively to treat such seizures is a difficult decision.

Neonatal seizures or electroconvulsive activity are usually the sign of neuronal compromise and the prognosis in large part will depend on any one of the many underlying causes of the seizure activity. Seizures in the neonatal period usually elicit an aggressive therapeutic response with administration of a variety of poorly evaluated drugs. This annotation explores recent evidence that the duration and frequency of the seizures may also have an additional harmful effect on outcome, with the consequence that effective anticonvulsant therapy may improve prognosis.

The incidence of seizures in the neonatal period is considerably higher than at any other time of life. Animal studies have shown that the immature brain is more prone to seizure activity than the mature brain, but paradoxically the immature brain appears to be less vulnerable than the adult brain to neuronal damage as a result of the seizures (see Holmes and Ben-Ari1 for review).

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The reason for the increased susceptibility of the immature brain to seizure activity is the developmental stage of opposing neuroexcitatory and neuroinhibitory activity, as GABAergic synapses are functionally more active than NMDA-AMPA ones and provide a net excitatory drive in the developing brain. In early life, GABA receptors have a mainly excitatory effect. This changes with progressive development when the sensitivity of the brain to seizures reduces.

An important concept of seizure susceptibility in the brain is kindling, and it is considered to be a more important factor in the immature than in the adult brain. Kindling refers to the effect of repeated but brief stimulation on a susceptible area of the brain, which produces an accelerating and prolonged effect resulting in generalised seizures. In a clinical context it has been suggested that kindling due to repeated subclinical stimuli may render a region of neurones epileptic. Repetitive seizures result in both a progressive increase in the duration of seizures and a decrease in the latency between seizures, and it has been shown in animal studies that kindling in the neonatal period results in an increased susceptibility to seizures later in life.2

WHAT CAN WE LEARN FROM ANIMAL EXPERIMENTS?

Until recently it has been difficult to extrapolate from animal studies the significance to the human neonatal brain of experimental seizure activity. Methodological problems included the nature of the experimental convulsions (prolonged seizure activity induced by chemical or electrical stimulation), the developmental age of the experimental animal, and the difficulty in understanding the effect on functional development as opposed to anatomical evidence of neuronal necrosis.

Recent advances in experimental design have thrown important new light on a number of these uncertainties. Frequent short lived convulsions have been produced by placing the neonatal rat pups (postnatal days 0–4) repeatedly in the volatile agent fluorothyl until both clinical and electroencephalographic (EEG) seizure activity was noted when they were withdrawn. This model allows the production of five short lived seizures per day for five days,3 which is much closer to the intermittent seizure disorder seen in premature and term neonates.

This model did not result in neuronal necrosis,4 but there was measurable morphological change involving cortical neuronal activation and density when the rat brains were examined in adult life,5 as well as significant functional adverse effects on the rats’ learning and memory when they reached maturity. In contrast, a single prolonged seizure in the neonatal period does not produce similar effects.6 Limited uncontrolled data in humans suggest that neonatal seizures may also have subtle long term adverse effects on various areas of cognitive function in children thought to be without overt neurological damage.7 Furthermore, status epilepticus in adolescent animals previously primed by short seizures in the neonatal period produced substantially increased neuronal loss.8 Severe convulsions in the adolescent period resulted in more neuronal damage than less prolonged seizures.

In summary, the experimental data support the contention that frequent, relatively short convulsions cause morphological changes in the immature brain which may affect subsequent behaviour. These changes may also increase the susceptibility to further brain damage if subsequent prolonged convulsions develop in later childhood.
Phenobarbitone has been reported to have adverse effects on the developing brain, including inhibition of brain growth, neuronal toxicity, and adverse cognitive and behavioural effects when administered to young animals. Phenobarbitone is not yet recommended for use in infants and neonates due to the lack of evidence for its efficacy and safety in this age group. However, it remains the mainstay of management of neonatal seizures.

A PRAGMATIC APPROACH

There is increasing evidence that neonatal seizures have a subtle but measurable adverse effect on neurodevelopmental progression and may predispose to cognitive, behavioural, or epileptic complications later in life. Modern and relatively simple devices such as the aEEG will allow earlier and more accurate recognition of electroconvulsive seizures and help to determine whether ambiguous clinical movements represent convulsions or not.

Unfortunately, we also know of no truly effective neonatal anticonvulsant while being concerned that phenobarbitone, the most widely used first line anticonvulsant, may actually compromise outcome because of its toxicity within the nervous system. How to respond to this dilemma of when to treat remains a major therapeutic conundrum.

It is my experience that neonatal convulsions tend to be overtreated in an attempt to abolish all evidence of seizure activity. As shown above, those babies with the most frequent seizures will be the ones most resistant to anticonvulsants. To resolve the problem of which anticonvulsants should be used to treat neonatal convulsions and at what dose, we must insist on more randomised controlled studies with reports on subsequent long term follow up. Without this evidence based data, the question cannot be definitively answered.

It is my practice to try to keep the number of different anticonvulsant drugs used in the management of neonatal seizures to a minimum. Prolonged neonatal seizures (longer than one minute) or frequent seizures (more than two in one hour) should be aggressively treated with phenobarbitone up to a maximum loading dose of 30 mg/kg in divided doses followed by a one off loading dose of phenytoin (20 mg/kg). Continued seizures may be best controlled by a continuous infusion of midazolam, which is becoming more widely used in the sedation of babies and children given intensive care and appears to have good safety margins. Seizures should not result in junior medical staff adding further and further anticonvulsants to the baby's medication, but each neonatal unit should develop a drug protocol based on a controlled and graded response to continuing convulsions.

The risk of seizure recurrence in children with neonatal seizures is relatively small, and, taking into account the potential toxicity of some anticonvulsant drugs, it seems good practice to stop anticonvulsant treatment as early as possible. My own practice is to withdraw anticonvulsants before discharge home if the baby is clinically neurologically normal on examination. In those that are discharged home on anticonvulsant treatment, withdrawal is undertaken at the earliest opportunity when clinical neurological recovery occurs. In persistently neurologically abnormal infants, anticonvulsants may be continued for up to six months but an attempt should be made to withdraw phenobarbitone by that time, and, if seizures recur, a more appropriate anticonvulsant should be introduced.

Author's affiliation

M Levene, Academic Unit of Paediatrics, Obstetrics and Gynaecology, University of Leeds, D Floor, Clarendon Wing, Leeds LS2 9NS, UK
REFERENCES


This month in the Archives of Disease in Childhood

The following papers appearing in the March 2002 issue of ADC may be of interest to readers of Fetal and Neonatal.


Controversy: Plagiocephaly and head binding. S J Bridges, T L Chambers, I K Pople, with commentary by S A Wall.